REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments, the following remarks and the attached Rule 132 Declaration of Patrice Mauriac, one of the inventors herein.

Applicants have amended claims 22 and 23 and such amendments are fully supported in the as-filed specification.

Claim 27 has been cancelled without prejudice or disclaimer.

Accordingly, the claims presently pending before the Examiner are 22-26, 28, 29 and 31-34.

Applicants have corrected the informality noted by the Examiner in the specification with respect the patent number so that it now reads correctly as 4,765,628. Thus, the objection has been overcome and should be withdrawn.

The objection to claim 27 has been rendered moot in view of its having been cancelled.

Claims 23-24, 27, 32 and 34 stand rejected under 35 USC § 112, second paragraph, as being indefinite. This rejection is respectfully traversed.

In amended claim 22, the subcutaneous implants comprise:

- a core (i) comprising at least one active principle dispersed in a polymeric matrix essentially consisting of PLGA, **wherein said active principle is at most 55% mass/mass of the total weight of the core**,

- a coating (ii) in film form comprising as the main component PLGA.

The amendment which introduces the expression "**wherein said active principle is at most 55% mass/mass of the total weight of the core**", finds its basis in all of the

Examples in the as-filed specification where it is disclosed that the active ingredient is at most 55% mass/mass of the total weight of the core. This means that such an amount is suitable for the purposes of the invention.

In amended claim 23, the expression "**selected from pharmaceutically acceptable bisphosphonic acids and their salts, vitamin D or analogues thereof and sex hormones**" has been introduced in order to clarify the nature of "active principle able to increase bone density" according to par. [0087], as requested by the Examiner.

In amended claim 24, the term "extremely" has been cancelled in order to remove any indefiniteness.

Claim 27 has been cancelled since it is redundant in view of claim 26.

Claims 32 and 34, which employ the open-ended language "comprised between" to define a molar ratio range and a thickness range, respectively, are, indeed, deemed to be boundless ranges on the basis of the description. Applicants definitely traverse this rejection as being groundless, since the meaning of said expression is nowhere intended to exclude the bounds. Furthermore, it should be borne in mind that the current Application is the US national phase of a PCT Patent Application for which the same expression did not raise any misinterpretation issue of the type raised herein. Therefore, Applicants are convinced that the ranges in claims 32 and 34 clearly and unambiguously include the bound values.

In the outstanding Office Action, claims 22, 25-27, and 31-32 stand rejected under 35 U.S.C. § 102(b) as being anticipated by **Wang et al.** This rejection is respectfully traversed.

In order to overcome this rejection, Applicants have amended the claims as noted above. Specifically, claim 22 has been amended by introducing the technical feature that the active principle is at most 55% mass/mass of the total weight of the core and by clarifying that the core is wholly coated by the coating.

In fact, as will be further explained hereafter, the subcutaneous implants of the present invention, not only are novel in view of the cited prior art documents, but also quite surprisingly, also show significant advantages in terms of the desired release profile of the active ingredient.

In the outstanding Office Action, the Examiner states that Wang et al. disclose an implant comprised of a core and a coating where the core contains PLGA and an active principle dispersed within it, while the coating is the same PLGA used in the core (p. 5 of the Office Action).

However, Wang et al. teach that **the implants must have a hole** drilled through the coating or even a hole drilled through the coating and the core, as is well represented in Fig. 1 of the Wang et al. reference (p. 1060), where CM1 and CM2 are referred to respectively.

Furthermore, it should be noted that in the core according to Wang et al., the active principle loading is never less than 70%, as indicated by Table 1 (p. 1061).

Accordingly, amended claim 22 distinguishes over Wang et al., since the claimed implants do not have any hole or an active principle loading of at most 55% mass/mass of the total weight of the core.

Moreover, amended claim 22 is also unobvious over Wang et al., as explained hereafter.

As summarised in the abstract provided at page 1059, Wang et al. are directed to implants for controlled release of 5-fluorouracil (5-FU) in the subconjunctival tissues, while minimizing the level of the same in other non-target ocular tissues. It is then specified that said release is dependent on a number of aspects, i.e. the lactide/glycolide ratio in the PLGA, the drug loading, the coating, the hole anatomy and the hole dimensions.

In this regard, the following, as shown in Figure 1, p. 1060, have been compared:

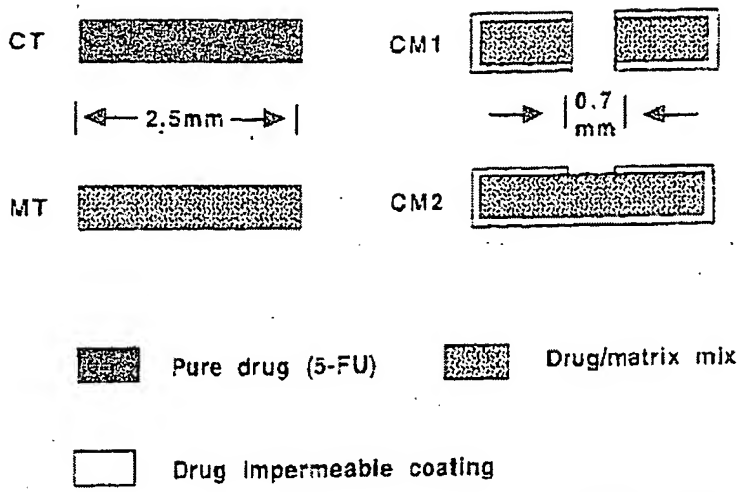

Fig. 1. Schematic representation of pure, matrix and coated implants. CT: pure drug only implant; MT: matrix implant; CM1: coated matrix implant with a hole drilled through the implant and coating; CM2: coated matrix implant with a hole drilled through the coating on one side.

The typical *in vitro* release profiles of the above four implants has been represented in Figure 2, wherein each matrix implant contains a 9:1 mass ratio of 5-FU to polymer. It is therefore shown that 5-FU rapidly dissolves from CT and MT (about 5 hours). The same drug dissolves almost completely over a period of 25 hours in the case of CM1, while 60% of the drug dissolves over the same period in the case of CM2.

It should be also noted that the coating, defined as impermeable, has been found to be intact at the end of the release study (see p. 1061, par. "In vitro release").

In the case of the *in vivo* study, reference is made to Figure 4, p. 1062, where it is shown that CM1 completes the drug release over a period of about 200 hours (i.e. less than 9 days), while the uncoated matrix MT completes the release over a period of about 100 hours (about 4 days).

In view of the foregoing, in the *Discussion* section, Wang et al. teach that "*a low drug to polymer ratio is undesirable in vivo because too much polymer would remain in the conjunctiva after the drug was exhausted. Incorporation of 5 mg of 5-FU would also result in too large an implant for subconjunctival implantation. From a clinical practice point of view, the ratio of drug to polymer is better kept as high as possible, i.e. 9:1.*

Coating such implants may prolong in vivo release of 5-FU for about 10 days. Although CM2 implants gave zero release profiles in vitro, they were not chosen for in vivo assessment since it is desirable to achieve therapeutic levels of 5-FU rapidly."

In this regard, it is clear that one of ordinary skill in the art would never have had any motivation to modify the implants of **Wang et al.** in the direction of the claimed invention, since it is evident that Wang et al. **teaches away from each and every technical aspect as claimed in the currently amended claim 22.**

As a matter of fact, Wang et al. teaches that:

- the drug/polymer mass ratio should be as high as possible;
- the drug release takes place through the drilled hole that can vary in depth and dimensions, but must be present otherwise the drug is confined within an **impermeable coating**; (in fact, the latter has proved to be **intact at the end of the release study**);
- the hole is an essential technical feature determining the extent of release, which in any event, is never higher than 10 days; and,
- CM1, i.e. the coated matrix implant with a hole drilled through the coating and matrix, is deemed to be preferred.

Therefore, one of ordinary skill in the art would never have even considered implants according to the claimed invention, since in view of Wang et al. there would have been no expectation of success in providing a core wherein the active principle is at most 55% mass/mass of the total weight of the core, or of providing a uniformly coated core by PLGA, thus **never needing nor teaching the making of a hole**. In fact, in view of the foregoing, the skilled person would have suggested, instead, to only modify the hole depth/dimensions in order to prolong the drug release.

By contrast, Applicants have most unexpectedly and surprisingly found that subcutaneous implants according to the claimed invention allow the achievement of a

very long term release of the active principle, even over a period of several months, and meet the requirements as mentioned in the description at par. [0037-0040]:

- does not allow the immediate dissolution of the active principle at time t = 0;
- release of the active principle through the core (i) and the coating (ii) by diffusion, and the resulting release rate by diffusion of the active principle has proven to be quite linear, confirming that it has been possible to reduce the **initial burst** which occurs in the first days after insertion of the implants themselves;
- after release by pure diffusion, the remaining amount of active principle and, consequently, the release rate is higher in the second phase of the active principle release; and,
- able to also limit the **second burst** caused by the disintegration of the core (i).

The technical results achieved and the versatility proven by the implants according to amended claim 22 would not have been derivable at all from the teaching of Wang et al.

The skilled person could not possibly expect that the claimed combination coating/core would influence the release kinetics of the active ingredient by **prolonging release over several months**, nor that the same implants would be able to give a **quite linear release profile** over the **whole release period**, with the implants showing a significant reduction in **both first and second burst effects**.

It is clear from the foregoing that the combination of the suitable core and coating features is absolutely not anticipated by Wang et al., as contended by the Examiner, and amended claim 22 is also unobvious over Wang et al.

Claim 22 is also rejected under 35 U.S.C. 103(a) as being unpatentable over **Chou et al.** This rejection is respectfully traversed.

Chou et al. disclose a PCL or PVAC matrix, while a coating of PLGA or EVA is applied by coextrusion. More clearly, the figures provided in this document refer to:

- the release of flucinolone acetonide (FA) from PCL matrix, drug loading 75% (Fig. 1),

- the release of flucinolone acetonide (FA) from PLGA matrix, drug loading 60% (Fig. 2),

- the release of flucinolone acetonide (FA) from PCL matrix, with and without PLGA skin, drug loading 60% (Fig. 3), and

- the release of flucinolone acetonide (FA) from PCL matrix, with and without PLGA skin, drug loading 40% (Fig. 4).

From said figures, it can be seen that **PCL** matrices (Fig. 1) provide for a **far better release profile** when compared to PLGA matrices (Fig. 2), even more so if one considers that the drug loading in the latter case is reduced with respect to the first one. This means that PCL (being more hydrophobic than PLGA) provides for a better control of the release of the (hydrophobic) active ingredient used, i.e. FA. Thus, the matrices containing PCL have been selected for making implants, and not containing PLGA, as illustrated in Figures 3 and 4.

In these figures, the performance of the matrices with PLGA skin is reported over a 2-month period and, for said period, it is readily observed that a PLGA skin can limit the release of the drug with respect to the matrices without a PLGA skin. However, it is important to note that only 15% of the drug is released after 2 months and **no information is given on what happens with the remaining 85% of the dose**. In fact, taking into account that PCL matrices are fully biodegradable, it is understandable that the drug present therein will, sooner or later, be entirely released.

Therefore, even if PLGA skin is found able to limit the drug release and reduce the initial burst, the later phases of the release are definitely left unknown, as well as being entirely unpredictable.

This means that a skilled person, wishing to achieve a prolonged **and** linear release profile over the **entire** drug release period, would never have found in Chou et al.

any suggestion or useful indication in that regard and thus would have never had any motivation to modify the teaching of Chou et al. in the direction of the claimed invention, which would be entirely contrary to Chou's belief that PCL is a better matrix that PLGA. Furthermore, in view of the fact that according to Chou et al. better results were obtained with a drug loading of 75% in a PCL matrix compared to a drug loading of 60% in a PLGA matrix, the skilled person would never have been taught how to release a **drug loading of not more than 55% in PLGA**, which are, indeed, **two of the essential features of amended claim 22**.

In view of this **clear teaching away**, it has been **absolutely unexpected** that implants having a core comprising at least one active principle dispersed in a polymeric matrix essentially consisting of **PLGA**, wherein said active principle is at most 55% mass/mass of the total weight of the core, and a coating comprising as the main component PLGA, wherein said core is wholly coated by said coating, as claimed in currently pending **claim 22**, to exhibit a very good linear release profile over a prolonged period of time. This is supported by all of the Examples, for instance, by Example 3 and related Figure 3B, where the **release profile** is advantageously **linear** and **does not show any burst** and the **entire release period** is observed to be about 350 days, i.e., **more than 11 months**!

In this regard, it has been proven that, in spite of the above teaching away by Chou et al., the inventors of the instant application by virtue of the claimed implants have surprisingly achieved technical results which not only are unexpected and not derivable from Chou et al., but also solve a technical problem that was not even addressed in Chou et al., other than the initial burst.

In order to provide further evidence of the non-obviousness of the claimed implants, a Declaration of Dr. Patrice Mauriac (Enclosure 3), who is one of the inventors, is enclosed herewith.

In said Declaration, the effect of three different drug loadings has been assessed in order to demonstrate that the initial burst is definitely not the sole technical aspect to consider in prolonged drug release implants.

At par. [0035] of Chou et al., it is stated that "*the burst release phase was less pronounced when FA levels (loading) in the PCL matrix were reduced from 75% to 60% or 40%*".

Having regard to the foregoing, a person of ordinary skill would never have considered the use of PLGA as matrix polymer for long term release implants.

However, if the skilled artisan had tried to follow the teaching of Chou et al., other than using PLGA in place of PCL he would have intuitively thought to further decrease the drug loading.

In order to test this view, Dr. Mauriac first provided three matrices as follows:

	Active ingredient	PLGA (L/G molar ratio 75/25 - molecular weight 115 kg/mol)
1	20%m/m	80%m/m
2	28%m/m	72%m/m
3	35%m/m	65%m/m

wherein each drug loading is significantly below the sole drug loading of 60% disclosed by Chou et al. with reference to the PLGA matrix (see Fig. 2).

This has been done to demonstrate that, even if the **skilled person** would have ignored the teaching away of Chou et al., thus trying to use PLGA in the matrix to verify the release profile over the **entire** drug release (not only for a period of 2 months), he **would have once again been led to the conclusion that PLGA is an entirely unsuitable matrix**, as explained below.

In this regard, the effect of three different drug loadings has been tested. From the graph reported in the Declaration (Figure A, p. 2), it can be observed that:

- the drug is released (and the polymeric matrix is fully destroyed) in about 200 days when the drug loading is comprised between 28% m/m and 35% m/m;

- by **decreasing the percentage of drug** within the matrix, a decrease of the initial release rate occurs. This is not a surprise as diffusion rate is known to depend on the concentration **but,**

- the decrease of the initial release rate later results in an **earlier and greater second burst**, thus leading to a **tri-phase release pattern limited to 160 days**, as is clear when a drug loading of 20% m/m is used.

Without wishing to be bound by any theory, it is believed that this is due to the chemistry of polyesters which produce acidic residues when the chains are hydrolyzed. If a large amount of drug is released from the matrix, then a large amount of outer medium penetrates into the matrix and simultaneously helps in getting these acidic residues out of the matrix itself. On the other hand, if only a small quantity of the drug leaves the core during the early stages, only a few acidic residues will leave the core. Accordingly, they will stay inside the core and help in cutting the remaining ester bonds (phenomenon called auto-catalysis).

Therefore, in view of the above, it can be observed that:

- when a **lower drug loading** is used, as in Figure A, where the PLGA matrices have a drug loading of 35%, 28%, 20%, respectively, the first burst is progressively reduced while an undesirable **second burst** progressively occurs which is earlier and greater,

- this reduction of the initial diffusion rate finally leads to a **shorter overall release duration** caused by an undesired earlier destruction of the polymeric matrix.

In this regard, it is evident that one of ordinary skill in the art would have been led to avoid the use of PLGA as a polymer matrix, since the above evidence would clearly discourage the use of same. As a matter of fact, the skilled man would indeed been aware of the fact that ***PLGA is an unsuitable matrix polymer for long term release implants.***

Moreover, it should be noted that Chou et al. only teach that PCL is preferred as a polymer for the matrix in connection with reducing the first burst effect, since only PCL matrices having drug loading of 75%, 60% and 40% are disclosed. Therefore, nothing useful is taught to the skilled person to modify this teaching in order to lead in the direction of the claimed invention.

Chou et al. also disclose to coat the PCL/FA core with PLGA. Even more so, the skilled person, taking into account the results shown in Figure A and the above discussion, would have been led to believe that, in the hypothetical case of using a PLGA matrix coated with PLGA:

- since the overall concentration of the drug with respect to the polymer had decreased, and
- the distance which the drug had to travel to leave the matrix had increased,

the initial diffusion rate (first burst) would have been further reduced (with respect to the uncoated matrix), consequently leading to a much shorter release duration caused by an undesirable much earlier destruction of the polymer in both the matrix and the coating.

In view of the fact that this eventuality is ***definitely undesirable*** insofar as long term release implants are concerned, the skilled person would once again have considered PLGA as absolutely unsuitable for use as the polymer for long term release implants.

Applicants are, therefore, completely convinced that the **implants** according to the current invention are highly **inventive (unobvious)**, since the combination of claimed features, i.e. a core comprising at least one active principle dispersed in a polymeric **matrix** essentially consisting of **PLGA**, wherein said **active principle is at most 55% mass/mass of the total weight of the core**, and a **coating** comprising as the main component **PLGA**, wherein said core is wholly coated by said coating, as claimed in amended **claim 22**, allows the achievement of the surprising **and entirely unexpected results found by Applicants, namely, a very prolonged and linear drug release profile until the entire drug is released**.

Claims 22, 26 and 28-29 are also rejected under § 103(a) in view of Chou et al. in combination with **Talton, Belenkaya et al.** and **Byon et al.** This rejection is traversed.

It is respectfully submitted that none of these prior art references provide any useful disclosure or technical information for overcoming the teaching away from the claimed invention by Chou et al. Specifically, in Chou et al. there is neither a suggestion nor a motivation to modify his disclosed structures which would lead in the direction of the claimed invention, in view of the following reasons:

- the high loading of the active principle;

- the combination of PLGA both in the core matrix and in the coating are never disclosed, nor, even more so, the drug loading of at most 55%; and,

- the supported teaching which discourages the use of PLGA as matrix, while teaching the use of PCL.

The Talton reference, in particular, has only been cited by the Examiner because PLGA is used in the coating, while Belenkaya et al. and Byon et al. are deemed to refer to coatings where both PLGA and PVP are present. Since Applicants are deemed to distinguish over this combination, withdrawal of the rejection is in order.

Claims 22 and 33-34 stand rejected under § 103(a) over Dorta et al. This rejection is traversed.

Dorta et al. has been cited as disclosing three stacked layers, the two external layers containing PLGA, while leaving 15% of the internal layer uncoated. In view of this teaching, Dorta et al. is clearly not relevant prior art with respect to the claimed invention. Since the claimed invention clearly distinguishes over Dorta et al., withdrawal of the rejection is solicited.

Claims 22-24 stand rejected under § 103(a) over Maquin et al. in view of Chou et al. This rejection is traversed.

Maquin et al. discloses compositions including PLGA and a peptide, thus failing to even implicitly suggest all of the features characterizing the claimed implants. It should be noted that according to Maquin et al.'s discussion with reference to the compositions disclosed therein (see page 4, lines 5-7), that "*this structure allows the peptide to be released in three stages, which are, respectively: pure diffusion, diffusion with swelling of the PLGA and release caused by PLGA degradation.*" Later on, at lines 16-24, it is further explained that:

"*The duration of this pure diffusion stage is essentially determined by the degree of heterogeneity of the dimensions of the peptide particles and the speed is essentially determined by the peptide content in the PLGA matrix.*

As a result of the wide diversity in the dimensions of the peptide granules, a sufficient quantity of peptide remains after the first stage of dissolution to be released over the subsequent stages.

In the second stage the peptide is released by diffusion with swelling of the polymer.

In the third stage, the residual peptide is released when the matrix is destroyed."

As explained above with reference to the enclosed Declaration, these types of compositions show a **tri-phase release pattern**, where not only a first burst but also an earlier and greater second burst can be observed, especially when the drug loading is reduced. This is also evidenced by Figures 3 and 4 of Maquin et al.

Therefore, the currently amended claim 22 distinguishes over the combination of Chou et al. in view of Maquin et al.

The Examiner has also rejected claims 22-25 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-3 of **US Patent 6,620,422** (Maquin et al.) in view of Chou et al..

As demonstrated above, currently amended claim 22 is patentable over the combination of Chou et al. and Maquin et al.. This is further supported by the fact that **no feature of amended claim 22 overlaps the compositions of claim 1 of US Patent 6,620,422**. As a matter of fact, those compositions only comprise a peptide having a particle size of 1 to 60 μm dispersed in a PLGA matrix.

Stated differently, the subcutaneous implants of the claimed invention according to claim 22 have a **core**, **wherein the active principle is at most 55% mass/mass of the total weight of the core**, and a **coating** in film form comprising as the main component PLGA, **wherein said core is wholly coated by said coating**.

Accordingly, since claims 22-25 completely distinguish over claims 1-3 of U.S. 6,620,422 in view of Chou et al., the non-statutory obviousness-type double patenting rejection has been overcome and should be withdrawn.

The standard to be employed in determining patentability is "preponderance of the evidence." Applicants' Rule 132 Declaration, which unequivocally demonstrates unexpected results, unquestionably rebuts the Examiner's determination of obviousness. Quite simply, the evidence submitted by Applicants is more convincing than the evidence offered in opposition thereto. *In re Oetiker*, 24 USPQ2d 1443 (Fed Cir. 1992).

Withdrawal of the objections and rejections is respectfully solicited and the issuance of a Notice of Allowance is respectfully requested.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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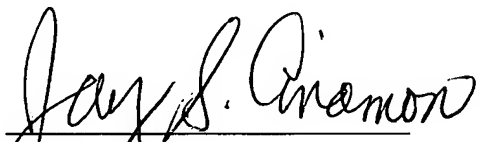
By 
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